



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. HYB-004US1)

In Re
Application of: Sudhir Agrawal) Group: 1623
Serial No.: 09/845,623) Examiner: McIntosh, T.C.
Filed: April 30, 2001)
Entitled: Modulation of Oligonucleotide)
Cpg-Mediated)
Immunostimulation by)
Positional Modification of)
Nucleosides)

DECLARATION PURSUANT TO 37 C.F.R. §1.132

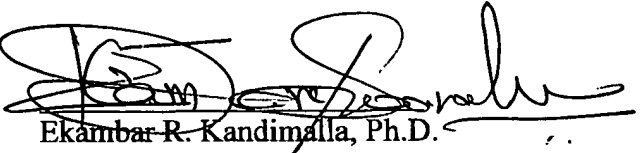
Hon. Assistant Commissioner for Patents:

I, Ekambar Kandimalla, Ph.D., hereby declare as follows:

1. I currently hold the position of Senior Director at Hybridon, Inc. ("Hybridon"). I am a named co-inventor on the above-identified application. I have previously submitted a declaration in the prosecution of this application on April 26, 2004. I incorporate the contents of that declaration by reference.
2. I understand that claims 18-24 and 27 of this application are rejected as not being enabled by the specification. I respectfully disagree.
- ✓ 3. Exhibit 1 shows the results of experiments conducted under my supervision, based upon the teachings of the specification. These results demonstrate that routine experimentation proves that nucleotide substitutions of 2'-deoxy-5-nitroindole, 2'-deoxy-3-nitropyrrole and 2'-deoxyuridine induce an improved immune response in a mouse model. It is my opinion that similar routine experimentation, as taught in the specification, would show similar results for the other modifications taught in the specification.

4. I hereby further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed:


Ekambar R. Kandimalla, Ph.D.

Dated:

July 21, 2005

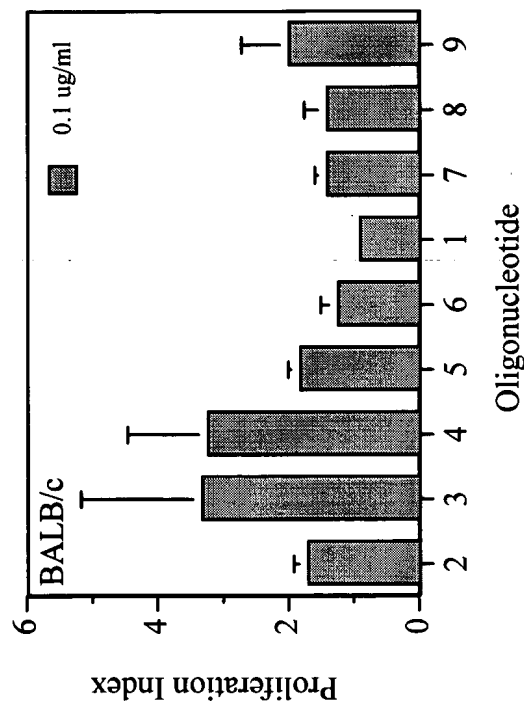


Exh. J

1	5'-TCCATGACGTTCCCTGATGC-3'
2	5'-TCXATGACGTTCCCTGATGC-3'
3	5'-TCCXTGACGTTCCCTGATGC-3'
4	5'-TCCAXGACGTTCCCTGATGC-3'
5	5'-TCCATXACGTTCCCTGATGC-3'
6	5'-TCCATGXCGTTCCCTGATGC-3'
7	5'-TCCATGACGXTCCTGATGC-3'
8	5'-TCCATGACGTXCCTGATGC-3'
9	5'-TCCATGACGTTXCTGATGC-3'

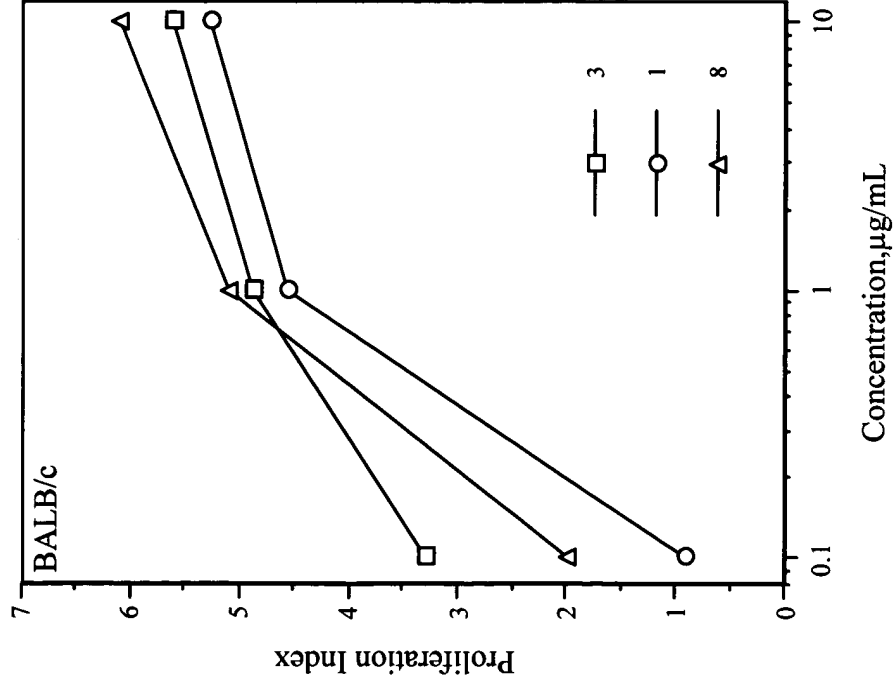
X = 2'-deoxy-5-nitroindole

BALB/c mouse spleen cell proliferation



Proliferation index at 24 hr at the indicated concentration

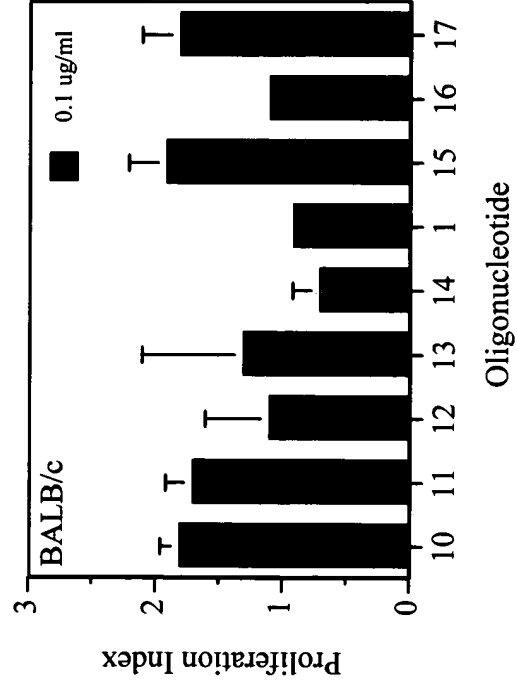
Dose-dependent BALB/c mouse spleen cell proliferation of representative compounds



1 5'-TCCATGACGTTCCCTGATGC-3'
10 5'-TCYATGACGTTCCCTGATGC-3'
11 5'-TCCYTGACGTTCCCTGATGC-3'
12 5'-TCCAYGACGTTCCCTGATGC-3'
13 5'-TCCATYACGTTCCCTGATGC-3'
14 5'-TCCATGYCGTTCCCTGATGC-3'
15 5'-TCCATGACGYTCCTGATGC-3'
16 5'-TCCATGACGTGCCCTGATGC-3'
17 5'-TCCATGACGTTYCTGATGC-3'

Y = 2'-deoxy-3-nitropyrrole

BALB/c mouse spleen cell proliferation

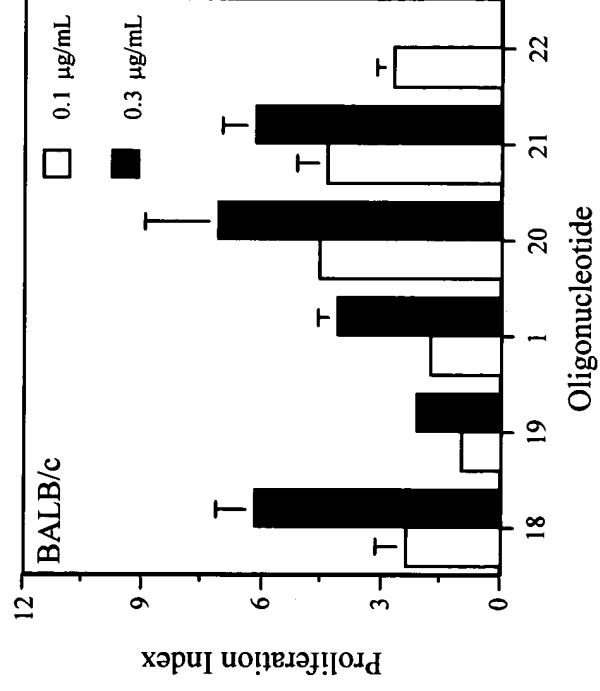


Proliferation index at 24 hr at the indicated concentration

1	5'-TCCATGACGTTCCCTGATGC-3'
18	5'-TCCATGUCGTTCCCTGATGC-3'
19	5'-TCCATUACGTTCCCTGATGC-3'
20	5'-TCCATGACGUTCCTGATGC-3'
21	5'-TCCATGACGTUCCCTGATGC-3'
22	5'-TCCATUACGTUCCCTGATGC-3'

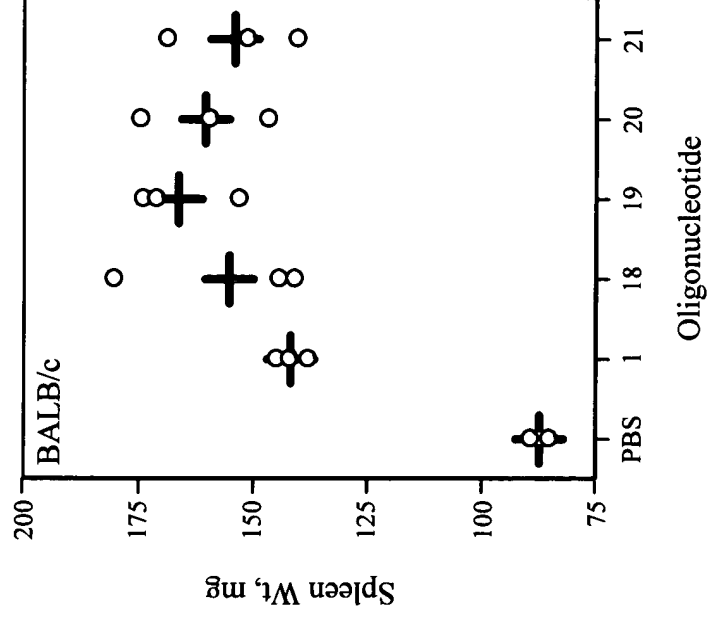
U = 2'-deoxyuridine

BALB/c mouse spleen cell proliferation



Proliferation index at 24 hr at the indicated concentrations

BALB/c mouse spleen enlargement

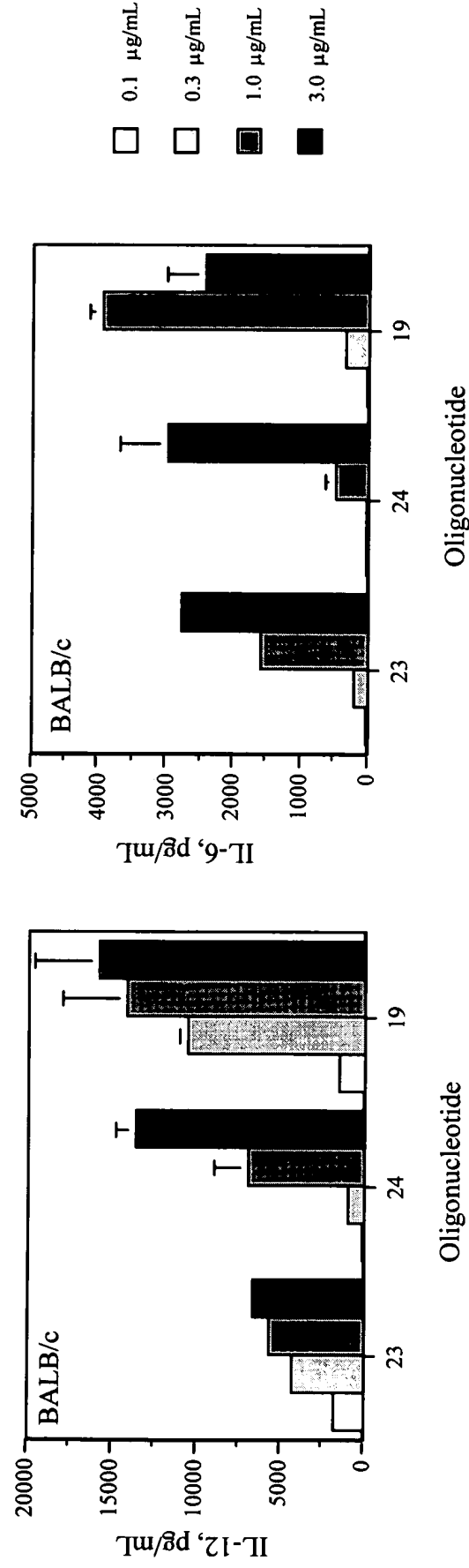


Mouse were given 5 mg/kg dose of oligos intraperitoneally and spleen weights were determined after 72 hrs

23	5'-CTATCTGACGTTCTCTGT-3'
24	5'-CCTACTAGCGTTCTCATC-3'
19	5'-TCCATUACGTTCCCTGATGC-3'

U = 2'-deoxyuridine

Cytokine induction profiles in BALB/c mouse spleen cell cultures



Spleen cells were stimulated with different concentrations of oligos for 24 hr and cytokine levels in supernatants were measured by ELISA.